10522227proviso

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:47:17 ON 09 FEB 2007

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 12:47:22 ON 09 FEB 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 FEB 2007 HIGHEST RN 920112-67-0
DICTIONARY FILE UPDATES: 8 FEB 2007 HIGHEST RN 920112-67-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

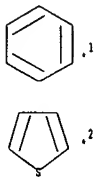
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

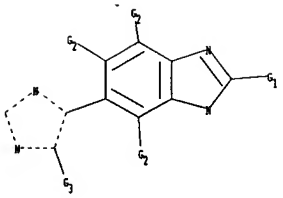
http://www.cas.org/ONLINE/UG/regprops.html

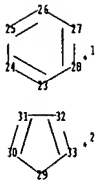
=>
Uploading C:\Program Files\Stnexp\Queries\10522227proviso.str

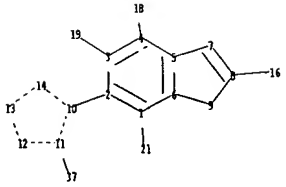
Karen Cheng

10522227proviso









chain nodes :
16 18 19 21 37
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 23 24 25 26 27 28 29 30 31 32 33
chain bonds :
1-21 2-10 3-19 4-18 8-16 11-37
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 8-9 10-11 10-14 11-12 12-13 13-14 23-24 23-28 24-25 25-26 26-27 27-28 29-30 29-33 30-31 31-32 32-33
exact/norm bonds :
1-21 3-19 4-18 5-7 6-9 7-8 8-9 8-16 10-11 10-14 11-12 11-37 12-13 13-14 29-30 29-33 30-31 31-32 32-33
exact bonds :
2-10
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 23-24 23-28 24-25 25-26 26-27 27-28
isolated ring systems :
containing 1 :

G1:X,H,N

G2:H,CH3

G3:[*1],[*2]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 16:CLASS 18:CLASS 19:CLASS 21:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 37:CLASS

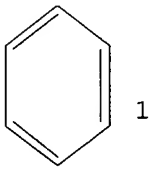
L1 STRUCTURE UPLOADED

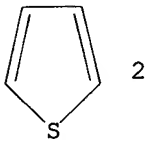
=> d

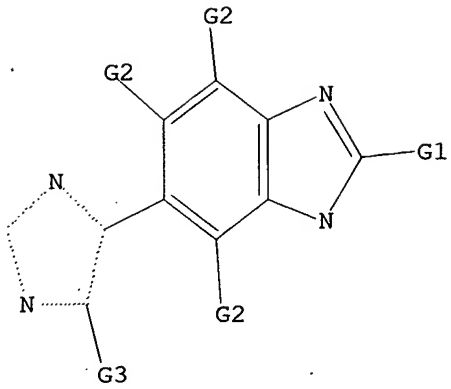
Karen Cheng

10522227proviso

L1 HAS NO ANSWERS
L1 STR







G1 X,H,N

G2 H,Me

G3 [@1],[@2]

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 12:47:44 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2014 TO ITERATE

100.0% PROCESSED 2014 ITERATIONS 464 ANSWERS
SEARCH TIME: 00.00.01

L2 464 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	172.10	172.31

FILE 'CAPLUS' ENTERED AT 12:47:48 ON 09 FEB 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Karen Cheng

10522227proviso

databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 9 Feb 2007 VOL 146 ISS 8
FILE LAST UPDATED: 8 Feb 2007 (20070208/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l2
L3 4 L2

=> d ibib abs hitstr tot

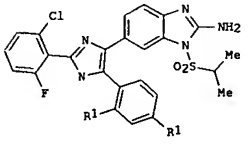
Karen Cheng

10522227proviso

=> d ibib abs tot

Karen Cheng

L3 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:349551 CAPLUS
DOCUMENT NUMBER: 145:62826
TITLE: Synthesis of imidazole based p38 MAP (mitogen-activated protein) kinase inhibitors under buffered conditions
AUTHOR(S): Magnus, Nicholas A.; Diseroad, William D.; Nevill, C. Richard, Jr.; Wepsiec, James P.
CORPORATE SOURCE: Chemical Product Research and Development Division, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Organic Process Research & Development (2006), 10(3), 556-560
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

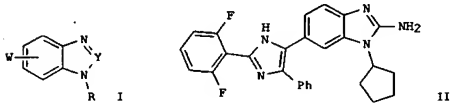
AB Chemical developed to give access to multigram quantities of imidazole 479754 and several related analogs, e.g., I (R1 = H or F) for Eli Lilly's p38 MAPK program targeting therapies to address inflammation was described. The mols. of interest had an iso-Pr sulfonyl group present on the 2-aminobenzimidazole heterocycle that was found to be labile when heated in polar solvents and/or exposed to high or low pH. Due to this instability issue, the syntheses of the target mols. required optimizing Sonogashira reaction conditions, employing a buffered oxidative method to produce α-diones, developing buffered reaction conditions to generate imidazoles, and developing final recrystn. conditions.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
prepd. as inhibitors of kinases, esp. p38 kinases. Exemplified compds. I showed inhibition for p38 kinase and suppression of TNF-α both in vitro and in vivo with IC50 values of ≤ 5 nM, < 100 nM and < 100 mg/kg, resp. Other biol. activities were also evaluated. Therefore, I and their pharmaceutical compns. are potentially useful for treating a disease or condition capable of being improved or prevented by inhibition of p38 kinase, such as cancer.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:962247 CAPLUS
DOCUMENT NUMBER: 143:266919
TITLE: Preparation of benzimidazole compounds as p38 kinase inhibitors for the treatment of cancer
INVENTOR(S): Bonjouklian, Rosanne; Dally, Robert Dean; De Dios, Alfonso; Del Prado Catalina, Miriam Filadelfa; Dominguez-Fernandez, Carmen; Jaramillo Aguado, Carlos; Lopez de Uralde-Garmendia, Beatriz; Montero Salgado, Carlos; Shepherd, Timothy Alan
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005080380	A1	20050901	WO 2005-US24	20050121
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1720862	A1	20061115	EP 2005-711246	20050121
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: EP 2004-380022 A 20040203
US 2004-563399P P 20040419
WO 2005-US24 W 20050121
OTHER SOURCE(S): MARPAT 143:266919
GI



I II

AB Benzimidazole compds. and their analogs I [wherein W = certain N-containing five-membered heteroaryl; Y = N, CH, CNH2 or CMe; R = alkyl, Ph, benzyl, etc., and pharmaceutically acceptable salts thereof], such as II, were

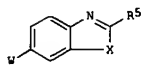
L3 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:159128 CAPLUS
DOCUMENT NUMBER: 142:348138
TITLE: Design of Potent and Selective 2-Aminobenzimidazole-Based p38α MAP Kinase Inhibitors with Excellent in Vivo Efficacy
AUTHOR(S): de Dios, Alfonso; Shih, Chuan; Lopez de Uralde, Beatriz; Sanchez, Concepcion; del Prado, Miriam; Cabrejas, Luisa M. Martin; Pleite, Sehila; Blanco-Urgoiti, Jaime; Lorite, Maria Jose; Nevill, C. Richard, Jr.; Bonjouklian, Rosanne; York, Jeremy; Vieth, Michal; Wang, Yong; Magnus, Nicholas; Campbell, Robert M.; Anderson, Bryan D.; McCann, Denis J.; Giera, Deborah D.; Lee, Paul A.; Schultz, Richard M.; Li, Li C.; Johnson, Lea M.; Wolos, Jeffrey A.
CORPORATE SOURCE: Lilly S.A., Eli Lilly and Co., Alcobendas, Madrid, 28108, Spain
SOURCE: Journal of Medicinal Chemistry (2005), 48(7), 2270-2273
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:348138
AB We report the design and discovery of a 2-aminobenzimidazole-based series of potent and highly selective p38α inhibitors. The lead compound had low-nanomolar activity in both ATP competitive enzyme binding and inhibition of TNFα release in macrophages. Compound showed excellent pharmacokinetics properties and oral activity in the rat collagen induced arthritis model compared with other p38 reference compds. A SAR strategy to address CyP3A4 liability is also described.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:143142 CAPLUS
DOCUMENT NUMBER: 140:199326
TITLE: Preparation of benzimidazoles and benzothiazoles as inhibitors of p-38 map kinase for treating metastasis or rheumatoid arthritis
INVENTOR(S): Bonjouklian, Rosanne; De Diego Gomez, Jose Eugenio; De Dios, Alfonso; Hamdouchi, Chafiq Hamdouchi; Li, Tiechao; Lopez De Uralde Garmendia, Beatriz; Vieth, Michal; York, Jeremy Schulenburg; Dally, Robert Dean; Del Prado Catalina, Miriam Filadelfa; Jaramillo, Carlos; Martin Cabrejas, Luisa Maria; Montero Salgado, Carlos; Pleite, Sheila; Sanchez-Martinez, Concepcion; Shepherd, Timothy Alan; Wikel, James Howard
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

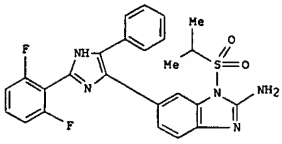
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014900	A1	20040219	WO 2003-US19890	20030731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003256297	A1	20040225	AU 2003-256297	20030731
EP 1554272	A1	20050720	EP 2003-784749	20030731
EP 1554272	B1	20061025		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
AT 343572	T	20061115	AT 2003-784749	20030731
US 2005272791	A1	20051208	US 2005-522227	20050125
PRIORITY APPLN. INFO.:			EP 2002-380178 A	20020809
			US 2002-421939P P	20021028
			WO 2003-US19890 W	20030731

OTHER SOURCE(S): MARPAT 140:199326
GI

L3 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



I

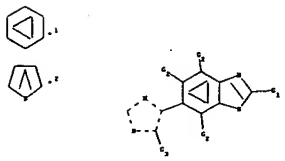


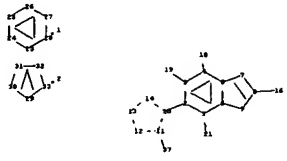
II

AB The present invention provides benzimidazoles and benzothiazoles (shown as I; W = imidazolyl, oxazolyl, pyrazolyl, oxopyrazolinyl, thiazolyl, 1,2,3-triazolyl, or imidazo[2,1-b]benzothiazolyl; X = NR4, S; R5 = halo, H, NR9R10; addnl. details are given in the claims; e.g. II) as p-38 map kinase inhibitors. The disclosed compds. inhibit p-38 kinase and are useful in the treatment of metastasis or rheumatoid arthritis. All exemplified I inhibit the p38 kinase enzyme with an IC50 of at least 5 μM. Four exemplified I were tested and found to suppress TNF-α in vitro with an IC50 <100 nM; three of these suppressed TNF-α in vivo in mice with an IC50 <100 mg/kg. Treatment of rats with II produced a dose-dependent inhibition of TNF-α synthesis, as measured in the synovial lavage fluid; the TMED50 = 10 mg/kg. II caused 54%, 73%, and 95% inhibition of lung metastasis formation for the 3, 10 and 30 mg/kg dose levels, resp., in the B16F10 melanoma lung metastasis model. II showed excellent dose-dependent activities against p38 MAPK in tumors harvested 2.5 h after dosing, seen as a dose-dependent inhibition of MAPKAP-K2 phosphorylation. II exhibited time- and dose-dependent inhibition of MAPKAP-K2 phosphorylation in P815 tumors in vivo. At all doses of II in a rat collagen induced arthritis efficacy model, there was a significant reduction in ankle diameter with a maximum reduction of 46% at 30 mg/kg; prednisolone reduced the inflammation to pre-arthritic levels. Although the methods of preparation are not claimed, preparative procedures and/or characterization data are given for 119 intermediates and 253 examples of I. For example, 1-isopropylsulfonyl-2-amino-6-[2-(thien-2-yl)-5-(phenyl)imidazol-4-yl]benzimidazole methanesulfonate was prepared in 97% yield by cyclizing thiophene-2-carboxaldehyde with 1-isopropylsulfonyl-2-amino-6-[α-[(tert-butyldimethylsilyl)oxy]-α-(phenyl)acetyl]benzimidazole in HOAc in the presence of Cu(OAc)2 and NH4OAc.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10522227proviso

```
=> fil reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      33.81     206.12

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -6.24      -6.24

FILE 'REGISTRY' ENTERED AT 12:49:52 ON 09 FEB 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     8 FEB 2007  HIGHEST RN 920112-67-0
DICTIONARY FILE UPDATES:    8 FEB 2007  HIGHEST RN 920112-67-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10522227proviso2.str
```





Karen Cheng

10522227proviso

chain nodes :
16 18 19 21 37
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 23 24 25 26 27 28 29 30 31
32 33
chain bonds :
1-21 2-10 3-19 4-18 8-16 11-37
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 8-9 10-11 10-14 11-12 12-13 13-14
23-24 23-28 24-25 25-26 26-27 27-28 29-30 29-33 30-31 31-32 32-33
exact/norm bonds :
1-21 3-19 4-18 5-7 7-8 8-16 10-11 10-14 11-12 11-37 12-13 13-14 29-30
29-33 30-31 31-32 32-33
exact bonds :
2-10 6-9 8-9
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 23-24 23-28 24-25 25-26 26-27 27-28
isolated ring systems :
containing 1 :

G1:X,H,N

G2:H,CH3

G3:[*1],[*2]

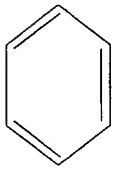
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 16:CLASS 18:CLASS 19:CLASS 21:CLASS 23:Atom
24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom
33:Atom 37:CLASS

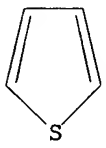
L4 STRUCTURE UPLOADED

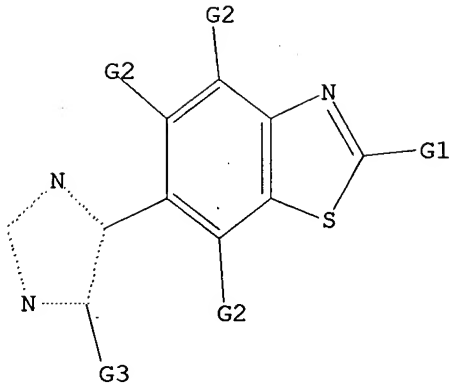
=> d
L4 HAS NO ANSWERS
L4 STR

Karen Cheng

10522227proviso







G1 X,H,N

G2 H,Me

G3 [@1],[@2]

Structure attributes must be viewed using STN Express query preparation.

=> s l4 full
FULL SEARCH INITIATED 12:50:12 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 143 TO ITERATE

100.0% PROCESSED 143 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L5 4 SEA SSS FUL L4

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	172.10	378.22

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-6.24

FILE 'CAPLUS' ENTERED AT 12:50:19 ON 09 FEB 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Karen Cheng

10522227proviso

held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 9 Feb 2007 VOL 146 ISS 8
FILE LAST UPDATED: 8 Feb 2007 (20070208/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l5
L6 1 L5

=> d ibib abs hitstr tot

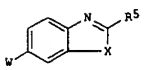
Karen Cheng

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN

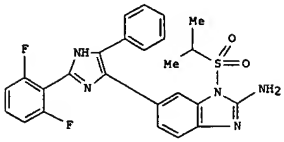
ACCESSION NUMBER: 2004:143142 CAPLUS
DOCUMENT NUMBER: 140:199326
TITLE: Preparation of benzimidazoles and benzothiazoles as inhibitors of p-38 map kinase for treating metastasis or rheumatoid arthritis
INVENTOR(S): Bonjouklian, Rosanne; De Diego Gomez, Jose Eugenio; De Dios, Alfonso; Hamdouchi, Chafiq Hamdouchi; Li, Tiechao; Lopez De Uralde Garmendia, Beatriz; Vieth, Michal; York, Jeremy Schulenburg; Dally, Robert Dean; Del Prado Catalina, Miriam Filadelfa; Jaramillo, Carlos; Martin Cabrejas, Luisa Maria; Montero Salgado, Carlos; Pleite, Sheila; Sanchez-Martinez, Concepcion; Shepherd, Timothy Alan; Wikel, James Howard
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014900	A1	20040219	WO 2003-US19890	20030731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003256297	A1	20040225	AU 2003-256297	20030731
EP 1554272	A1	20050720	EP 2003-784749	20030731
EP 1554272	B1	20061025		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
AT 343572	T	20061115	AT 2003-784749	20030731
US 2005272791	A1	20051208	US 2005-522227	20050125
PRIORITY APPLN. INFO.:			EP 2002-380178 A	20020809
			US 2002-421939P P	20021028
			WO 2003-US19890 W	20030731

OTHER SOURCE(S): MARPAT 140:199326
GI



I



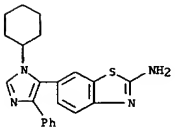
II

AB The present invention provides benzimidazoles and benzothiazoles (shown as I; W = imidazolyl, oxazolyl, pyrazolyl, oxopyrazolinyl, thiazolyl, 1,2,3-triazolyl, or imidazo[2,1-b]benzothiazolyl; X = NR4, S; R5 = halo, H, NR9R10; addnl. details are given in the claims; e.g. II) as p-38 map kinase inhibitors. The disclosed compds. inhibit p-38 kinase and are useful in the treatment of metastasis or rheumatoid arthritis. All exemplified I inhibit the p38 kinase enzyme with an IC50 of at least 5 μM. Four exemplified I were tested and found to suppress TNF-α in vitro with an IC50 <100 nM; three of these suppressed TNF-α in vivo in mice with an IC50 <100 mg/kg. Treatment of rats with II produced a dose-dependent inhibition of TNF-α synthesis, as measured in the synovial lavage fluid; the TMED50 = 10 mg/kg. II caused 54%, 73%, and 95% inhibition of lung metastasis formation for the 3, 10 and 30 mg/kg dose levels, resp., in the B16F10 melanoma lung metastasis model. II showed excellent dose-dependent activities against p38 MAPK in tumors harvested 2.5 h after dosing, seen as a dose-dependent inhibition of MAPKAP-K2 phosphorylation. II exhibited time- and dose-dependent inhibition of MAPKAP-K2 phosphorylation in P815 tumors in vivo. At all doses of II in a rat collagen induced arthritis efficacy model, there was a significant reduction in ankle diameter with a maximum reduction of 46% at 30 mg/kg; prednisolone reduced the inflammation to pre-arthritic levels. Although the methods of preparation are not claimed, preparative procedures and/or characterization data are given for 119 intermediates and 253 examples of I. For example, 1-isopropylsulfonyl-2-amino-6-[2-(thien-2-yl)-5-(phenyl)imidazol-4-yl]benzimidazole methanesulfonate was prepared in 97% yield by cyclizing thiophene-2-carboxaldehyde with 1-isopropylsulfonyl-2-amino-6-[α-[(tert-butyldimethylsilyl)oxy]-α-(phenyl)acetyl]benzimidazole in HOAc in the presence of Cu(OAc)2 and NH4OAc.

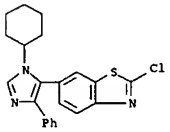
IT 660435-94-9P, 2-Amino-6-[1-cyclohexyl-4-(phenyl)imidazol-5-yl]benzothiazole 660435-95-0P, 2-Chloro-6-[1-cyclohexyl-4-(phenyl)imidazol-5-yl]benzothiazole
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(drug candidate; prepn. of benzimidazoles and benzothiazoles as inhibitors of p-38 map kinase for treating metastasis or rheumatoid arthritis)

RN 660435-94-9 CAPLUS
CN 2-Benzothiazolamine, 6-(1-cyclohexyl-4-phenyl-1H-imidazol-5-yl)- (9CI) (CA INDEX NAME)

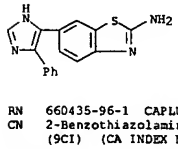


RN 660435-95-0 CAPLUS
CN Benzothiazole, 2-chloro-6-(1-cyclohexyl-4-phenyl-1H-imidazol-5-yl)- (9CI) (CA INDEX NAME)



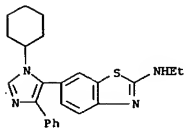
IT 660435-93-8P, 2-Amino-6-(5-phenylimidazol-4-yl)benzothiazole 660435-96-1P, 2-Ethylamino-6-[1-cyclohexyl-4-(phenyl)imidazol-5-yl]benzothiazole
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of benzimidazoles and benzothiazoles as inhibitors of p-38 map kinase for treating metastasis or rheumatoid arthritis)

RN 660435-93-8 CAPLUS
CN 2-Benzothiazolamine, 6-(5-phenyl-1H-imidazol-4-yl)- (9CI) (CA INDEX NAME)



RN 660435-96-1 CAPLUS
CN 2-Benzothiazolamine, 6-(1-cyclohexyl-4-phenyl-1H-imidazol-5-yl)-N-ethyl- (9CI) (CA INDEX NAME)

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Karen Cheng